Amendments to the Claims:

All amendments and cancellations to the claims are made without prejudice or disclaimer. This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (currently amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

providing an ensemble of related protein backbone structures;

selecting a plurality of variable positions in said ensemble of related protein backbone structures;

selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures;

applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures;

sampling each amino acid in said set of amino acids at each variable position in each variant protein sequence;

evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures; and

generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in

said ensemble of related protein backbone structures to generate a total probability for each of said amino acids; and

   generating an output of the probability matrix.

2.   (currently amended) ~~A method according to claim 1 further comprising the step of:~~ A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

   providing an ensemble of related protein backbone structures;

   selecting a plurality of variable positions in said ensemble of related protein backbone structures;

   selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures;

   applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures;

   sampling each amino acid in said set of amino acids at each variable position in each variant protein sequence;

   evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures; ~~and~~

   generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids; and

   generating a ~~single~~ at least one protein sequence from said probability matrix; and

   generating an output of the at least one protein sequence.

3. (currently amended) ~~A method according to claim 1 further comprising the step of: producing~~ A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

    providing an ensemble of related protein backbone structures;

    selecting a plurality of variable positions in said ensemble of related protein backbone structures;

    selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures;

    applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures;

    sampling each amino acid in said set of amino acids at each variable position in each variant protein sequence;

    evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures; ~~and~~

    generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids; and

    generating a combinatorial library of proteins from said probability matrix; and

    generating an output of the combinatorial library.

4. (currently amended) A method according to claim [[1]] 3 wherein said steps are repeated more than once to generate said probability matrix

5.   (currently amended) A method according to claim [[1]] 3 wherein said protein design algorithm comprises an optimization procedure selected from the group of: dead end elimination algorithm; genetic algorithm; Monte Carlo algorithm; and self consistent mean field theory algorithm or combinations thereof.

6.   (currently amended) A method according to claim [[1]] 3 wherein at least one backbone structure of the ensemble is derived from the structure of a natural protein.

7.   (currently amended) A method according to claim [[1]] 3 wherein at least one backbone structure of the ensemble is generated by comparative modeling.

8-13.   (cancelled)

14.   (currently amended) A method according to claim [[1]] 3 wherein said ensemble of related backbone structures comprises backbone structures of a family of natural proteins.

15.   (currently amended) A method according to claim [[1]] 3 wherein said ensemble of related backbone structures is derived from an NMR structure.

16.   (currently amended) A method according to claim [[1]] 3 wherein said ensemble of related protein backbone structures is generated by a Monte Carlo simulation.

17.   (currently amended) A method according to claim [[1]] 3 wherein said ensemble of related protein backbone structures is generated by a molecular dynamics simulation.

18.   (currently amended) A method according to claim [[1]] 3 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

19 - 37. (cancelled)

38.   (currently amended) A method according claim 2 wherein the amino acid sequence of the ~~single~~ at least one protein sequence is selected by identifying the amino acid with the lowest free energy at each position.

39.   (currently amended) A method according claim [[1]] 3 further comprising selecting an upper limit on free energy, allowing amino acid variations among amino acids that are below the upper free energy limit, and generating [[a]] the combinatorial library of protein sequences from said probability matrix.

40.   (currently amended) A method according claim [[1]] 3 further comprising incorporating amino acids at incrementally lower probabilities until a desired complexity is achieved, and generating a library of protein sequences from said probability matrix.

41.   (previously presented) A method according to claim 18 wherein the at least two constraints comprise a first constraint corresponding to a first structural form and second constraint corresponding to a second structural form that is distinct from the first structural form.

42.   (previously presented) A method according to claim 18 wherein the at least two probability matrices are combined by adding or subtracting free energies values from said probability matrices.

43.   (previously presented) A method according to claim 18 wherein the combining process is iterated.

44.   (currently amended) The method of claim [[1]] 3 wherein the sampling an amino acid position comprises freezing side chain identities and rotamers at positions in the protein other than the sampled amino acid position.

45.   (currently amended) The method of claim [[1]] 3 wherein the probability matrix is expressed as a set of partition functions.

46.   (currently amended) The method of claim [[1]] 3 wherein the probability matrix is expressed as a free energy value.

47.   (previously presented) The method of claim 1 wherein the probability matrix comprises information for all twenty amino acids.

48.   (currently amended) The method of claim [[3]] 61 further comprising screening or selecting one or more proteins from the library for a desired property.

49.   (previously presented) The method of claim 4 wherein, in a subsequent cycle, the protein design algorithm uses the probability matrix from a previous cycle.

50.   (previously presented) The method of claim 48 wherein the screening or selecting comprises identifying a protein with enhanced catalytic activity or altered specificity, relative to an initial protein whose backbone structure is one of the backbone structures of the ensemble.

51-59. (cancelled)

60.   (currently amended) A method of providing a protein, the method comprising:
        performing the method of claim 1;
providing an ensemble of related protein backbone structures;

selecting a plurality of variable positions in said ensemble of related protein backbone structures;

selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures;

applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures;

sampling each amino acid in said set of amino acids at each variable position in each variant protein sequence;

evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures; ~~and~~

generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids; and

producing at least one protein comprising a sequence based on said probability matrix.

61. (currently amended) A method of providing a protein library, the method comprising:

~~performing the method of claim 1;~~ providing an ensemble of related protein backbone structures;

selecting a plurality of variable positions in said ensemble of related protein backbone structures;

selecting a set of amino acids to computationally test at each of said variable positions in said backbone structures;

applying to each protein backbone structure in said ensemble of related protein backbone structures a protein design algorithm to generate at least one variant protein sequence for each of said protein backbone structures;

sampling each amino acid in said set of amino acids at each variable position in each variant protein sequence;

evaluating the energetic fitness of each amino acid in said set of amino acids at each of said variable positions in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures; and

generating a probability matrix by combining said energetic fitness of each of said amino acids in each of said variant protein sequences for each of said protein backbone structures in said ensemble of related protein backbone structures to generate a total probability for each of said amino acids; and

producing a library of proteins that include proteins that each comprise a sequence based on said probability matrix.

62- 66. (cancelled)

67.   (currently amended) The method of claim [[1]] 3 wherein the step of sampling and evaluating fitness of one or more amino acids comprises sampling and evaluating fitness of different rotamers of the one or more amino acids at position in at least one backbone structure.

68.   (currently amended) The method of claim 2 further comprising producing a protein that comprises the single at least one protein sequence.